CASE STUDY:
**OLIVIA, 8, ALL**

# VOD WITH RENAL AND PULMONARY DYSFUNCTION

## following HSCT in a pediatric patient with relapsed acute lymphoblastic leukemia (ALL)

Data based on actual patient case experiences. Disease progression may vary and may not be indicative of all patients. Individual diagnosis and treatment decisions are at the discretion of the healthcare provider.

## Indication

Defitelio® (defibrotide sodium) is indicated for the treatment of adult and pediatric patients with hepatic VOD, also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following HSCT.

## IMPORTANT SAFETY INFORMATION

### Contraindications

Defitelio is contraindicated in the following conditions:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

**Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.**

HSCT=hematopoietic stem-cell transplantation; VOD=veno-occlusive disease (also known as sinusoidal obstruction syndrome, or SOS).

DEFITELIO® (defibrotide sodium) injection 80 mg/mL

# PATIENT HISTORY OF PRESENT ILLNESS

## Olivia, an 8-year-old female with relapsed high-risk pre–B-cell ALL

### PHYSICAL EXAM

- Vital signs within normal range
- No hepatomegaly
- No ascites
- Performance score: 80%
- Pre-HSCT abdominal ultrasound not performed

### TREATMENT APPROACH

- Admitted for allogeneic HSCT 3.5 years post initial diagnosis, following therapy for second CNS relapse
  - CNS negative; MRD 0%, in remission
- Matched unrelated (10/10) T-cell–replete allogeneic HSCT
  - Conditioning regimen: TBI + etoposide
  - GvHD prophylaxis: tacrolimus + methotrexate
  - VOD prophylaxis: ursodiol

### RISK FACTORS FOR DEVELOPING VOD[1-5]

- Performance score <90%
- Advanced disease
- Use of hepatotoxic drugs
- Iron overload
- Allogeneic HSCT
- Myeloablative conditioning regimen
- High-dose TBI-based conditioning regimen

# IMPORTANT SAFETY INFORMATION

## Warnings and Precautions

**Hemorrhage**

Defitelio may increase the risk of bleeding in patients with VOD after HSCT. Do not initiate Defitelio in patients with active bleeding. Monitor patients on Defitelio for signs of bleeding. If bleeding occurs, withhold or discontinue Defitelio.

Concomitant systemic anticoagulant or fibrinolytic therapy may increase the risk of bleeding and should be discontinued prior to Defitelio treatment. Consider delaying Defitelio administration until the effects of the anticoagulant have abated.

**Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.**

CNS=central nervous system; GvHD=graft-vs-host disease; MRD=minimal residual disease; TBI=total body irradiation.

# ADMISSION BASELINE (DAY -8)

### PHYSICAL EXAM

- Weight: 20.3 kg
- Vital signs normal
- No hepatomegaly, no ascites
- Performance score: 80%
- Abdominal girth: 51.5 cm
- $O_2$ saturation on RA: 100%

| RELEVANT LABORATORY FINDINGS | |
|---|---|
| **Total serum bilirubin** | 0.4 mg/dL |
| **Liver biochemistry** | ALP: 171 U/L<br>AST: 68 U/L[a]<br>ALT: 40 U/L |
| **Serum creatinine** | 0.4 mg/dL |
| **CBC** | WBC: 2.7 x $10^9$/L[a]<br>Hemoglobin: 8.2 g/dL[a]<br>Hematocrit: 26.5%[a]<br>Platelets: 158,000/mcL[a] |
| **Ferritin** | 1260 ng/mL[a] |

[a]Denotes lab values outside the reference range as defined by Mayo Clinic Laboratories, with the exception of ferritin (defined by University of Rochester Medical Center).[6-8]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; RA=room air; WBC=white blood cell.

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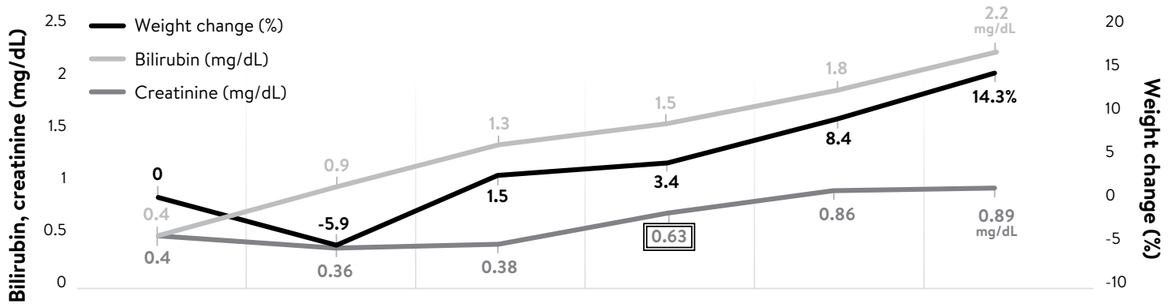
# CASE SUMMARY




| BASELINE: DAY -8 | DAY +4 | DAY +9 | DAY +10 | DAY +12 | DAY +13 |
|---|---|---|---|---|---|
| AST: 68 U/L[a] | | | AST: 100 U/L[a]<br>ALT: 85 U/L[a] | AST: 709 U/L[a]<br>ALT: 486 U/L[a] | AST: 741 U/L[a]<br>ALT: 546 U/L[a] |
| | | Mild abdominal tenderness | RUQ pain | ▸ | Severe RUQ pain |
| | | | Hepatomegaly | • | Hepatomegaly |
| | | | Ascites–mild | ▸ | Ascites–severe |
| | | | Platelet-refractory thrombocytopenia | • | Platelet-refractory thrombocytopenia |
| | | | $O_2$ saturation on RA: 93% | ▸ | Decreased $O_2$ saturation at rest |
| | | | Decreased urinary output | • | Decreased urinary output |
| | | | | Reversal of portal flow | Reversal of portal flow |

Admitted to PICU

- Met Cairo/Cooke diagnostic criteria for VOD[9]
- Met EBMT diagnostic criteria for VOD[10,11]
- First evidence of renal/pulmonary dysfunction[12-14]
- ▸ Symptom worsened
- • Symptom remained the same

No change in weight or bilirubin from Day +7 to Day +8.

[a]Denotes elevated lab value.[6]

EBMT=European Society for Blood and Marrow Transplantation; PICU=pediatric intensive care unit; RUQ=right upper quadrant.

# ADDITIONAL CONSIDERATIONS

**Day +9** – Patient presented with mild abdominal tenderness

**Day +10** – Patient had elevated AST and ALT,[6] right upper quadrant pain, platelet-refractory thrombocytopenia, $O_2$ saturation of 93% on room air, and decreased urinary output. Hepatomegaly and ascites were confirmed by ultrasound

- Differential diagnosis included: hyperacute GvHD, drug toxicity, infection, fluid overload, VOD, engraftment syndrome
- Patient met Cairo/Cooke diagnostic criteria for VOD with right upper quadrant pain, hepatomegaly, ascites, and platelet-refractory thrombocytopenia.[9] Patient also met EBMT diagnostic criteria for VOD with hepatomegaly, ascites, and platelet-refractory thrombocytopenia[10,11]
- Patient showed first evidence of renal and pulmonary dysfunction with creatinine 1.5 x baseline, decreased urinary output, and oxygen saturation of 93% on room air[12-14]

**Day +12** – Patient had worsening AST, ALT, right upper quadrant pain, and ascites as well as decreasing $O_2$ saturation on room air. Patient also had continued hepatomegaly, platelet-refractory thrombocytopenia, and decreased urinary output. There was reversal of portal flow

- Differential diagnosis included: acute GvHD, drug toxicity, infection, fluid overload, VOD, engraftment syndrome

**Day +13** – Patient had worsening AST, ALT, right upper quadrant pain, and ascites. Patient also had continued hepatomegaly and platelet-refractory thrombocytopenia as well as decreased urinary output and $O_2$ saturation at rest. Reversal of portal flow persisted

- Differential diagnosis included: acute GvHD, drug toxicity, infection, fluid overload, VOD, multi-organ failure
- Patient admitted to PICU for management of fluid balance

# IMPORTANT SAFETY INFORMATION

## Warnings and Precautions

### Hypersensitivity Reactions

Hypersensitivity reactions including rash, urticaria, and angioedema have occurred in less than 2% of patients treated with Defitelio. One case of an anaphylactic reaction was reported in a patient who had previously received Defitelio. Monitor patients for hypersensitivity reactions, especially if there is a history of previous exposure. If a severe hypersensitivity reaction occurs, discontinue Defitelio, treat according to the standard of care, and monitor until symptoms resolve.

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# RECENT ADVANCES IN DIAGNOSTIC CRITERIA FOR VOD DIAGNOSIS

Historically, the Baltimore and modified Seattle criteria have been used for diagnosis of VOD[15-17]

### EBMT diagnostic criteria for VOD in children

| THE EBMT CRITERIA FOR CHILDREN DO NOT INCLUDE A LIMITATION FOR TIME OF VOD ONSET | |
|---|---|
| **The presence of 2 or more of the following is required[10,a]:** | **Implementation guidance from Mahadeo et al:** |
| • Unexplained consumptive and transfusion-refractory thrombocytopenia[b] | • Defined as a CCI of <5000-7500 following ≥2 sequential ABO-compatible fresh platelet transfusions[11] |
| • Otherwise unexplained weight gain on 3 consecutive days, despite the use of diuretics, or weight gain >5% above baseline value | |
| • Hepatomegaly above baseline value (best if confirmed by imaging)[c] | • Defined as an absolute increase of ≥1 cm in liver length at the midclavicular line; if a baseline measurement is not available, can be defined as >2 SDs above normal for age[11] |
| • Ascites above baseline value (best if confirmed by imaging)[c] | • Mild (minimal fluid by liver, spleen, or pelvis), moderate (<1 cm fluid), or severe (fluid in all 3 regions with >1 cm fluid in at least 2 regions). When feasible, baseline ultrasound should be used to identify increased ascites[11] |
| • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥2 mg/dL within 72 hours | |
| | • Liver biopsy, portal venous wedge pressure, and reversal of portal venous flow on Doppler ultrasonography should not be used for the routine diagnosis of VOD in children, adolescents, and young adults[11]<br>• Use of a structured radiologic reporting template is recommended when there is clinical concern for VOD[11] |

***These proposed criteria have not been prospectively validated in clinical trials***

[a]With the exclusion of other potential differential diagnoses.

[b]≥1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines.

[c]Suggested: imaging (US, CT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites.

CCI=corrected count increment; CT=computed tomography; MRI=magnetic resonance imaging; SD=standard deviation; US=ultrasonography.



# CAIRO/COOKE DIAGNOSTIC CRITERIA FOR VOD

| REVISED DIAGNOSTIC CRITERIA FOR ADULT AND PEDIATRIC PATIENTS[9] | | |
|---|---|---|
| ***Any 2* of the following after HSCT[d]:** | **OR** | ***Any 1* of the following after HSCT[d]:** |
| • Elevated bilirubin (≥2 mg/dL) or greater than upper institutional limits[e]<br>• Unexpected weight gain (≥5% compared to baseline weight pre-HSCT)<br>• Excessive platelet transfusions consistent with refractory thrombocytopenia post HSCT<br>• Hepatomegaly for age or increased size over pre-HSCT<br>• Right upper quadrant pain<br>• Ascites confirmed by physical exam and/or imaging studies<br>• Reversal of portal venous flow (hepatofugal flow) by Doppler ultrasound | | • Hepatic biopsy consistent with VOD<br>• Unexplained elevated portal venous wedge pressure<br><br>Though it is not recommended, a liver biopsy or direct portal wedge pressure measurements can be used when making a diagnosis of VOD, if necessary[9] |

***These proposed criteria have not been prospectively validated in clinical trials***

# IMPORTANT SAFETY INFORMATION

## Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

**Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.**

[d]Probably or definitely secondary to VOD/SOS and not other etiologies.[9]

[e]In patients with an already elevated bilirubin prior to HSCT conditioning, this criterion should not be utilized in the diagnostic criteria.[9]

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# EFFICACY OF DEFITELIO WAS EVALUATED IN 689 PATIENTS[18,19]

**STUDIES INCLUDED A BROAD RANGE OF ADULT AND PEDIATRIC PATIENTS WITH VOD WITH RENAL OR PULMONARY DYSFUNCTION FOLLOWING HSCT[18-20]**

| | Study 1[13,18] | Study 2[18,21] | Study 3[18-20] |
|---|---|---|---|
| **Study design** | Phase 3 prospective | Phase 2 prospective | Expanded access study |
| **Number of patients** | **102** | **75** | **512** |
| **VOD associated with:** | Multi-organ dysfunction (pulmonary, renal, or both)[a] | Multi-organ dysfunction[b] | Renal or pulmonary dysfunction[c] |
| **Median age (years) (range)** | 21 (<1, 72) | 32 (<1, 61) | 14 (<1, 69) |
| **Type of transplant, n (%)** **Allogeneic** **Autologous** | 90 (88) 12 (12) | 67 (89) 8 (11) | 450 (88) 61 (12) |
| **Ventilator or dialysis dependent at study entry, n (%)** | 34 (33) | 8 (11) | 225 (42) |
| **Median number of days on treatment (days) (range)** | 21.5 (1, 58) | 19.5 (3, 83) | 21.0[d] (1, 91) |
| **Treatment dose of Defitelio** | 6.25 mg/kg infusion every 6 hours | | |

[a]A diagnosis of VOD was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: hepatomegaly, ascites, and weight gain >5% by Day +21 post HSCT).[18]

[b]A diagnosis of VOD was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: ascites, weight gain >5% from baseline, hepatomegaly, or right upper quadrant pain) by Day +35 post HSCT.[21]

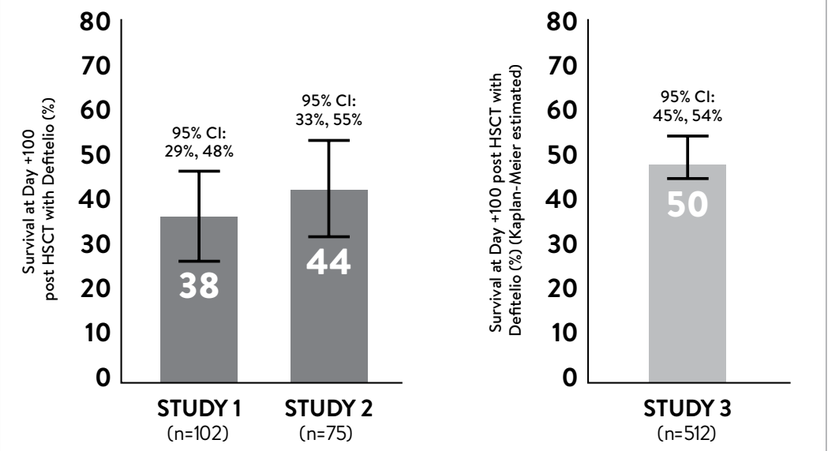
[c]A diagnosis of VOD was made using Baltimore criteria (bilirubin ≥2 mg/dL and at least 2 of the following: hepatomegaly, ascites, and weight gain >5%) by Day +35 post HSCT or modified Seattle criteria (presentation by Day 20 post HSCT of at least 2 of the following: bilirubin >2 mg/dL, hepatomegaly or right upper quadrant pain, and weight gain >2% of baseline).[16,19,22]

[d]Duration of treatment from first dose to last dose is presented because days without treatment were not captured for the expanded access study.



# DEFITELIO WAS PROVEN TO IMPROVE SURVIVAL AT DAY +100 CONSISTENTLY ACROSS 3 STUDIES[18,19]

**SURVIVAL AT DAY +100 POST HSCT WITH DEFITELIO ACROSS STUDIES IN ADULT AND PEDIATRIC PATIENTS[18,19]**




**Expected Day +100 survival with supportive care: 21% to 31%**
Based on published reports and analyses of patient-level data for individuals with hepatic VOD with renal or pulmonary dysfunction who received supportive care or interventions other than Defitelio[18]

## DRUG INTERACTIONS[18]

- Defitelio may enhance the pharmacodynamic activity of antithrombotic/fibrinolytic drugs such as heparin or alteplase. Concomitant use of Defitelio with antithrombotic or fibrinolytic drugs is contraindicated because of an increased risk of hemorrhage

## IMPORTANT SAFETY INFORMATION

### Contraindications

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- Concomitant administration with systemic anticoagulant or fibrinolytic therapy
- Known hypersensitivity to Defitelio or to any of its excipients

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CI=confidence interval.

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# DELAYS IN DEFITELIO INITIATION WERE ASSOCIATED WITH INCREASED MORTALITY AT DAY +100[18,19]

## IN AN EXPLORATORY POST HOC ANALYSIS FROM STUDY 3[18,19]

- Analysis of Study 3 indicated that **increased mortality at Day +100 was associated with longer delays in Defitelio administration** following a diagnosis of VOD with renal or pulmonary dysfunction (confirmed by the Cochran-Armitage trend test; *P*<0.001)
  - Analysis based on adult and pediatric patients (n=512) with a diagnosis of VOD with renal or pulmonary dysfunction
  - The reason for initiation delay following diagnosis was not assessed in this expanded access study

# SAFETY PROFILE

**ADVERSE REACTIONS INDEPENDENT OF CAUSALITY ANY GRADE ≥10% OR GRADE 4–5 ≥2% OF DEFITELIO-TREATED PATIENTS[18,a]**

| Adverse reaction | Defitelio (n=176) n (%) | |
|---|---|---|
| | Any grade | Grade 4–5[b] |
| **Hypotension** | 65 (37) | 12 (7) |
| **Diarrhea** | 43 (24) | 0 |
| **Vomiting** | 31 (18) | 0 |
| **Nausea** | 28 (16) | 0 |
| **Epistaxis** | 24 (14) | 0 |
| **Pulmonary alveolar hemorrhage** | 15 (9) | 12 (7) |
| **Gastrointestinal hemorrhage** | 15 (9) | 5 (3) |
| **Sepsis** | 12 (7) | 9 (5) |
| **Graft-vs-host disease** | 11 (6) | 7 (4) |
| **Lung infiltration** | 10 (6) | 5 (3) |
| **Pneumonia** | 9 (5) | 5 (3) |
| **Pulmonary hemorrhage** | 7 (4) | 4 (2) |
| **Infection** | 6 (3) | 4 (2) |
| **Hemorrhage intracranial** | 5 (3) | 4 (2) |
| **Hyperuricemia** | 4 (2) | 4 (2) |
| **Cerebral hemorrhage[c]** | 3 (2) | 3 (2) |

**Please see additional Important Safety Information on page 13 and accompanying full Prescribing Information.**

[a]Excludes events considered to be due to the underlying disease: multi-organ failure, veno-occlusive disease, respiratory failure, renal failure, and hypoxia.

[b]Adverse reactions considered life-threatening or fatal.

[c]Cerebral hemorrhage has been included in the table due to clinical relevance.

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# TREATMENT MODIFICATIONS FOR SPECIFIC EVENTS OR PROCEDURES

**TREATMENT MODIFICATIONS FOR TOXICITY OR INVASIVE PROCEDURES[18]**

| Event | Recommended action |
|---|---|
| **Hypersensitivity reaction**<br>• Severe or life-threatening (anaphylaxis) | **1.** Discontinue Defitelio permanently; do not resume treatment. |
| **Bleeding**<br>• Persistent, severe, or potentially life-threatening | **1.** Withhold Defitelio.<br>**2.** Treat the cause of bleeding and give supportive care as clinically indicated.<br>**3.** Consider resuming treatment (at the same dose and infusion volume) when bleeding has stopped and the patient is hemodynamically stable. |
| • Recurrent significant bleeding | **1.** Discontinue Defitelio permanently; do not resume treatment. |
| **Invasive procedures** | **1.** There is no known reversal agent for the profibrinolytic effects of Defitelio. Discontinue Defitelio infusion at least 2 hours prior to an invasive procedure.<br>**2.** Resume Defitelio treatment after the procedure, as soon as any procedure-related risk of bleeding is resolved. |

## Indication

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# IMPORTANT SAFETY INFORMATION

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## Warnings and Precautions

### Hemorrhage

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## Most Common Adverse Reactions

The most common adverse reactions (incidence ≥10% and independent of causality) with Defitelio treatment were hypotension, diarrhea, vomiting, nausea, and epistaxis.

**Please see accompanying full Prescribing Information.**

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**For additional information, visit defitelio.com**
**or call Jazz Pharmaceuticals Customer Service at 1-800-833-3533.**

**References: 1.** Center for International Blood & Marrow Transplant Research. Appendix L: Karnofsky/Lansky performance status. https://www.cibmtr.org/manuals/fim/1/en/topic/appendix-l-karnofsky-lansky-performance-status. Accessed July 31, 2020. **2.** Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2015;50(6):781-789. **3.** Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51(7):906-912. **4.** Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. *Biol Blood Marrow Transplant.* 2016;22(3):400-409. **5.** Corbacioglu S, Jabbour EJ, Mohty M. Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Biol Blood Marrow Transplant.* 2019;25(7):1271-1280. **6.** Mayo Clinic. Pediatric test reference values. https://www.mayocliniclabs.com/test-info/pediatric/refvalues/reference.php. Accessed August 13, 2020. **7.** Mayo Clinic. Pediatric test reference values. https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/113357. Accessed August 13, 2020. **8.** University of Rochester Medical Center. Ferritin (blood). https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=ferritin_blood. Accessed August 13, 2020. **9.** Cairo MS, Cooke KR, Lazarus HM, et al. Modified diagnostic criteria, grading classification and newly elucidated pathophysiology of hepatic SOS/VOD after haematopoietic cell transplantation. *Br J Haematol.* 2020;190(6):822-836. **10.** Corbacioglu S, Carreras E, Ansari M, et al. Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2018;53(2):138-145. **11.** Mahadeo KM, Bajwa R, Abdel-Azim H, et al; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network; Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation. Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: an international expert position statement. *Lancet Haematol.* 2020;7(1):e61-e72. **12.** Carreras E. How I manage sinusoidal obstruction syndrome after haematopoietic cell transplantation. *Br J Haematol.* 2015;168(4):481-491. **13.** Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood.* 2016;127(13):1656-1665. **14.** Ng CK, Chan MH, Tai MH, et al. Hepatorenal syndrome. *Clin Biochem Rev.* 2007;28(1):11-17. **15.** Carreras E. Early complications after HSCT. In: Apperley J, Carreras E, Gluckman E, et al, eds. *The EBMT Handbook.* 6th ed. Paris, France: European School of Haematology; 2012:176-195. **16.** Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation.* 1987;44(6):778-783. **17.** McDonald GB, Sharma P, Matthews DE, et al. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology.* 1984;4(1):116-122. **18.** Defitelio [package insert]. Palo Alto, CA: Jazz Pharmaceuticals. **19.** Kernan NA, Grupp S, Smith AR, et al. Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome. *Br J Haematol.* 2018;181(6):816-827. **20.** Data on file. DEF-2018-022. Palo Alto, CA: Jazz Pharmaceuticals. **21.** Richardson PG, Soiffer RJ, Antin JH. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* 2010;16(7):1005-1017. **22.** McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med.* 1993;118(4):255-267.

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